Applicants have canceled claims 2, 3, 8, 9, 19-24, and 26-33, which are directed to non-elected inventions.

A "marked up" version of the amended claims, showing the changes made, is attached.

Summary of the Office Action

Claims 1, 4-7, 10-18, and 25 were examined in this case. Claims 1, 5, 7, and 15 are rejected under 35 U.S.C. § 102(b). Claims 1, 3, 5, 15, and 25 stand rejected under 35 U.S.C. § 102(a). Claims 1, 4-7, 10-18, and 25 are rejected under 35 U.S.C. §§ 101 and 112, first and second paragraphs. Each of the rejections levied in the Office Action is addressed individually below in the order in which they appear in the Office Action.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 5, 7, and 15 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number U00047. The Examiner states that claims 1 and 7 are drawn to a substantially pure nucleic acid encoding a LIN-37 polypeptide, and as such, read on a cosmid, in that the cosmid has been isolated and purified beyond the genomic material found in a cell, and contains the gene from the LIN-37 protein. The Examiner further states that claim 15 is drawn to a vector comprising the nucleic acid of claim 1, and as such, does not exclude other nucleic acids or genes. This rejection is addressed as follows.

Claim 1 has been amended herewith to recite a substantially pure nucleic acid encoding a LIN-37 polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, where the polypeptide has about 50% or greater amino acid sequence

identity to SEQ ID NO: 1, and also has the ability to alter cell proliferation. Similarly, claim 7 has been amended to recite a substantially pure DNA encoding the amino acid sequence of SEQ ID NO: 1 that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, wherein the DNA encodes a polypeptide having the ability to alter cell proliferation.

The present amendment incorporates part of the definition of "substantially pure" (defined in the specification at page 12, lines 8-10) into claims 1 and 7 and makes it clear that the nucleic acid encoding the LIN-37 polypeptide is free from the genes that flank the *lin-37* gene in the naturally-occurring genome of the organism. In the cosmid disclosed as Accession number U00047, the *lin-37* gene is not free of the genes which, in the naturally-occurring genome of the organism, flank the gene. For example, the sequence disclosed by Accession Number U00047 contains "2.2 Mb of contiguous nucleotide sequence from chromosome II of *C. elegans,*" which is contained in a cosmid called ZK418. In addition, the NCBI (National Center for Biotechnology Information) database lists nine sequences predicted to be contained within the ZK418 cosmid (ZK418.1, ZK418.2, ZK418.3, ZK418.4, ZK418.5, ZK418.6, ZK418.7, ZK418.8, ZK418.9) (a copy of this web page was submitted with the response of April 13, 2000).

Based on these facts and the amendment to the claims, it is clear that the *lin-37* gene sequence contained in cosmid ZK418, is not "free of genes, which in the naturally occurring genome of the organism from which the DNA of the invention is derived, flank the gene," as required by the present claims. Thus Applicants assert that claims 1 and 7, as amended herewith, as well as claims 5 and 15, which depend from claim 1, are novel. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(a)

Claims 1, 3, 5, 15, and 25 remain rejected under 35 U.S.C. 102(a) as being anticipated by Lu and Horvitz (June 1996 meeting); Ceol and Horvitz (June 1996 meeting); Lu and Horvitz (May 1997 meeting); and Ceol and Horvitz (May 1997 meeting). The Examiner states that "others" is defined in terms of "inventive entity" and that in the instant application, the inventive entity consists of Horvitz, Ceol, and Lu. The Examiner further asserts that in the prior art cited in the 102(a) rejections, none of the inventive entities consisted of Horvitz, Ceol, and Lu, therefore the prior art cited for the 102(a) rejection in Paper No: 11 constitutes proper prior art. Applicants address this rejection as follows.

The requirements for joint inventorship are set forth in M.P.E.P. 2137.01. It is stated under "REQUIREMENTS FOR JOINT INVENTORSHIP" that

> "The inventive entity for a particular application is based on some contribution to at least one of the claims made by each of the named inventors. 'Inventors may apply for a patent jointly even though
> (A) they did not physically work together or at the same time,
> (B) each did not make the same type or amount of contribution, or
> (C) each did not make a contribution to the subject matter of every claim of the patent.'"

Joint inventors may make different contributions to the same application. Therefore, it is possible that a particular aspect of the invention may be disclosed in a reference published by fewer than all of the inventors. This does not classify the reference as "by another" because only the individuals named as inventors are authors of the reference. In contrast, if someone other than an inventor on the joint application for patent were named as an author on the reference, the reference would classify as "by another," provided that the person(s) other than one of the inventors were not "working under the direction and supervision of the inventor" (see M.P.E.P.

2132.01 and *In re Katz* 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

Publications of Lu and Horvitz (June 1996 meeting); Ceol and Horvitz (June 1996 meeting); and Ceol and Horvitz (May 1997 meeting)

Applicants submit that, in reference to Lu and Horvitz (June 1996 meeting); Ceol and Horvitz (June 1996 meeting); and Ceol and Horvitz (May 1997 meeting), the Examiner is misinterpreting the definition of "inventive entity" as an entity where fewer than all the inventors are named as authors on a reference. A prior art reference that names fewer than all of the inventors, but only persons who are inventors, is a disclosure of Applicants' own work. As stated under 102(a), if Applicant's disclosure of his or her own work is within the year before the application filing date, it cannot be used against him or her under 35 U.S.C. § 102(a) (see M.P.E.P. 2132.01 and *In re Katz* 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Applicants also note that the dates of these abstracts are less than one year before the filing date of May 28, 1997 of provisional application (U.S.S.N. 60/047,996), from which the present application claims benefit. Accordingly, these references do not qualify as prior art to the claimed invention.

The Lu et al. Publication (June 1997)

The authors of the fourth cited reference, Lu et al. (June 1997), are Xiaowei Lu, Jeff H. Thomas, and Bob Horvitz. As stated in the attached Declaration of Drs. H. Robert Horvitz, Craig Ceol, and Xiaowei Lu, (unsigned; an executed Declaration will be filed as soon as it is available) to which the Examiner is now directed, the experiments described in the Lu et al. abstract publication that relate to the invention were the joint contributions of the instant

notwithstanding inventors alone, the inclusion of an additional author on the publication. The Lu et al. abstract discloses the cloning of three Class B synMuv genes, *lin-37*, *lin-35*, and *lin-53*. The claimed invention is to nucleic acids encoding a LIN-37 polypeptide. Publication authors Xiaowei Lu and Bob Horvitz contributed toward the cloning and characterization of *lin-37,* and are named as inventors of the present application. The other named author, Jeff H. Thomas, contributed to worked involving *lin-53*, but did not contribute to the cloning and characterization of *lin-37*, as claimed in the present application. Thus Jeff Thomas's contribution to the publication of Lu et al. concerned subject matter which is not claimed in the present application.

In light of the above comments, Applicants assert that relative to the above-cited publications, which are describing Applicants' own work, inventorship is correct as to the inventive entity. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 101

Claims 16 and 17 stand rejected under 35 U.S.C. § 101 on the assertion that the claimed invention is directed to non-statutory subject matter. The Examiner states that the claims, as written, embrace natural cells within a body. Claim 16 has been amended herewith to recite a cell which contains a substantially pure nucleic acid encoding a lineage-37 (LIN-37) polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, where the polypeptide has about 50% or greater amino acid sequence identity to SEQ ID NO: 1, and where the polypeptide has the ability to alter cell proliferation. Claim 16, as

amended herewith, does not recite a product as it occurs in nature. Furthermore, claim 17, which depends from claim 16, and is subject to the limitations of claim 16, also does not encompass a product of nature. Accordingly, Applicants respectfully request that the rejection of claims 16 and 17 be withdrawn.

Claims 1, 4-7, 10-18, and 25 stand rejected under 35 U.S.C. § 101 on the assertion by the Examiner that the claimed invention is not supported by a specific and substantial utility. The Examiner states that neither the specification nor any art of record teaches a function of the isolated nucleic acids of SEQ ID NO: 2, or nucleic acids having 50% homology to SEQ ID NO: 2 beyond the encoding of a synMuv polypeptide. The Examiner further asserts that the specification does not teach a specific and substantial utility for the synMuv polypeptides, and does not teach a relationship to any specific diseases or establish a molecular mechanism or empirical association linking the synMuv polypeptides to the etiology of any specific diseases. Lastly, the Examiner asserts that there is no evidence of record that there is any demonstrated real world use for the LIN-37 protein obtained from *C. elegans*, concluding that the asserted utilities are speculative. This rejection is respectfully traversed.

Applicants assert that the presently claimed invention is supported by a specific and substantial utility. According to the Revised Interim Utility Guidelines, "specific utility" means a utility that is specific to the subject matter claimed. The Guidelines, at pages 5 to 6, state that "a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed." The Guidelines also define "substantial utility" as " a utility that defines a 'real world' use." Page 28 of the Guidelines uses as an example of a "substantial utility" a cure for a disease being a

desirable outcome based upon a need in the art, and states that a claimed protein that can cure Alzheimer's disease is a substantial and "real world" utility of that protein.

Applicants assert that the presently claimed invention has a specific utility. The specification, at page 18, lines 17-20, states that synMuv polypeptides act to negatively regulate vulval induction, and the specification, at page 8, lines 18-20, further states that the synMuv polypeptides of the invention may be used to modulate cell proliferation by administering to a cell a proliferation-modulating amount of a synMuv polypeptide. It has been well established throughout the specification that *C. elegans* synMuv mutants display phenotypes in which cell proliferation is excessive, and that synMuv polypeptides (including LIN-37) have been demonstrated to rescue this phenotype. For example, the specification, at page 20, lines 14-19, discloses that a cDNA was isolated from the Okkema embryonic cDNA library that is about 950 bp in size and can rescue the *lin-37* Muv phenotype when expressed under the control of the *col-10* promoter (*col-10* encodes a cuticle collagen and is highly expressed in the hypodermis and its precursor cells). The specification, at page 19, lines 12-13, further states that compounds which block the Muv phenotype of synMuv mutant animals are potential antitumor agents. LIN-37 has clearly been shown to rescue the Muv phenotype, as described above, and accordingly, can be used as an antitumor agent.

Since LIN-37 has been shown by Applicants to negatively regulate cell proliferation in *C. elegans*, and known diseases, for example, cancer are characterized by excessive cell proliferation, Applicants contend that the invention, as recited in claims 1, 4-7, 10-18, and 25 has a specific utility, that is for the treatment of a tumor or cancer, using a LIN-37 polypeptide, or a gene encoding a LIN-37 polypeptide.

Turning to the Examiner's statement that the claimed invention does not have a substantial utility, Applicants assert that a cure for cancer is a desirable outcome based upon a well-established need in the art. Thus, Applicants assert that the disclosed use of a LIN-37 polypeptide is substantial.

In light of these comments, Applicants assert that a specific and substantial utility of the *lin-37* or synMuv nucleic acids, polypeptides, and cells containing such nucleic acids and polypeptides of claims 1, 4-7, 10-18, and 25 has been established, and withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 4-7, 10-18, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, based on the assertion in the Office Action that since the claimed invention is not supported by a well established utility, for the reasons set forth in the rejection under discussed under 35 U.S.C. § 101, one skilled in the art clearly would not know how to use the claimed invention. Applicants have addressed the rejection of claims 1, 4-7, 10-18, and 25 under "Rejections Under 35 U.S.C. § 101," to which the Examiner is now directed.

Claims 1, 4-7, 10-18, and 25 also stand rejected under 35 U.S.C. § 112, first paragraph, on the assertion by the Examiner that the specification does not reasonably provide enablement for nucleic acids that encode nucleic acid variants having at least 50% nucleic acid sequence identity to SEQ ID NO: 1. Specifically, the Examiner states that the specification does not discuss departures from the nucleic acid sequence of SEQ ID NO: 2. The Examiner further states that polynucleotides that would not encode proteins that share either structural or

functional properties with LIN-37 are encompassed by claim 10. In addition, the Examiner states that the specification fails to provide guidance for how one would use such polynucleotides. And the Examiner states that the specification fails to provide working examples which would provide guidance to one skilled in the art on how to use the broadly claimed polynucleotides. The specific aspects of the rejection are addressed as follows.

Regarding the Examiner's assertion that the specification does not discuss departures from the nucleic acid sequence of SEQ ID NO: 2, Applicants contend that the claims, as amended herewith, point out the extent or type of functional and physical properties that the claimed nucleic acids must have. First, independent claims 1, 16, and 18 recite nucleic acids encoding LIN-37 polypeptides, wherein the polypeptides share about 50% or greater amino acid sequence identity to SEQ ID NO: 1. Claim 7 recites DNA encoding the amino acid sequence of SEQ ID NO:1 (LIN-37), and claim 10, as amended herewith, recites a substantially pure synMuv nucleic acid comprising nucleic acid having about 50% or greater nucleotide sequence identity to the DNA sequence of SEQ ID NO:2. In addition, claim 25, as amended herewith, also recites a substantially pure *lin-37* nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO:2. Thus, all of the independent claims of the invention recite required physical properties. Moreover, each of claims 1, 7, 10, 16, 18, and 25 further recites a functional limitation by clearly setting forth that the nucleic acids of claims 1, 7, 10, 16, 18, and 25 encode polypeptides capable of altering cell proliferation.

The above-described guidelines can be used to identify polynucleotides, as recited in the claims as amended herewith. The specification teaches that *lin-37* genes may be identified by (1) identifying a nucleic acid having structural similarity to at least a portion of a *lin-37* gene or

lin-37 gene mutant; and (2) testing the function of the putative *lin-37* gene or *lin-37* gene mutant.

With respect to step (1) of identifying *lin-37* genes or *lin-37* gene mutants, the specification provides the sequence of the *lin-37* gene and the encoded polypeptide. In addition, the specification clearly defines a substantially pure nucleic acid encoding a LIN-37 polypeptide having "about 50% or greater amino acid sequence identity" to LIN-37, and also teaches how one of ordinary skill in the art might identify such a sequence (see, page 10, line 21 to page 11, line 13). In light of these teachings, Applicants submit that any person skilled in the art of gene cloning would be able to identify a sequence having about 50% or greater nucleotide sequence identity to a given sequence, particularly the *lin-37* gene sequence.

With respect to step (2) of identifying *lin-37* genes or *lin-37* gene mutants, the specification sets forth that a synMuv gene is "characterized by the ability to modulate cell proliferation and having at least 10%, preferably 30%, and most preferably 50% amino acid sequence identity to at least one of the synMuv proteins described herein below" and also states that "[r]epresentative members of the synMuv gene family include, the *lin-37*, . . . gene of *C. elegans*, . . ." may also encode a "polypeptide which modulates cell death (inhibiting or enhancing) in a cell or tissue when provided by other intracellular or extracellular delivery methods" (page 9, lines 10-15). The specification defines the phrase "modulating cell proliferation" to mean, "increasing or decreasing the number of cells which undergo cell division in a given cell population or altering the fate of a given cell" (page 10, lines 8-10). The specification further defines a The specification further teaches that "the degree of modulation provided by a synMuv or modulating compound in a given assay will vary, but that one skilled in the art can determine the statistically significant change in the level of cell proliferation which

identifies a synMuv or a compound which modulates a synMuv" (page 10, lines 10-14).

Based on the teaching of the specification, Applicants contend that one skilled in the art could have tested the function of a polypeptide encoded by a putative *lin-37* gene. There is no reason to doubt the assertion that additional synMuv family member genes having identity in structure and function to *lin-37* can be identified as set forth in the specification.

To specifically address the Examiner's concern that polynucleotides that would not encode proteins that share either structural or functional properties with LIN-37 are encompassed by claim 10, Applicants note that claim 10 has been amended to recite, "A substantially pure synMuv nucleic acid comprising nucleic acid having about 50% or greater nucleotide sequence identity to the DNA sequence of SEQ ID NO:2, wherein said nucleic acid encodes a polypeptide having the ability to alter cell proliferation." By definition (see the specification at page 9, lines 10-21) the identified synMuv polynucleotides would encode polypeptides that share both structural and functional properties with LIN-37. Accordingly, this aspect of the rejection may be withdrawn.

In response to the Examiner's statement that the specification fails to provide working examples, Applicants contend that no working example is required. Applicants point out that the Federal Circuit has made clear the level of teaching needed to enable a claim with respect to the number of working examples, and has stated that a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. See *In re Walter L. Borkowski and John J. Van Venrooy*, 422 F2d 904, 164 UPSQ 642 (Fed. Cir. 1970) (11 step method for preparing an oxygenated hydrocarbon, found to be enabled by the specification absent a working example).

See also *In re Roger A. Long*, 368 F.2d 892, 151 USPQ 640 (Fed. Cir. 1966). ("The absence of a working example, denominated as such, does not compel the conclusion that a specification does not satisfy the requirement of 35 USC 112...").

In light of the above comments, withdrawal of this aspect of the rejection is respectfully requested.

Claims 1, 4-6, 10-18, and 25 stand further rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is addressed as follows.

Pages 7-9 of The Interim Written Description Guidelines presents a decision tree for use in determining if a claim meets the written description requirement. Applicants submit that, according to the guidance provided in the decision tree, Applicants were in possession of the invention at the time the application was file, as addressed in detail below.

In accordance with the Guidelines, the specification clearly states that synMuv nucleic acids and polypeptides, and more specifically *lin-37* nucleic acids and polypeptides, that alter cell proliferation are essential to the operation/function of the claimed invention. Methods for obtaining a nucleic acid sequence that encodes a polypeptide having at least 50% or greater nucleotide sequence identity to SEQ ID NO:1 (*lin-37*), as recited in independent claims 1, 16, and 18, and for obtaining a nucleic acid sequence having at least 50% or greater nucleotide sequence identity to SEQ ID NO:1 (*lin-37*), as recited in independent claims 10 and 25, are conventional in the art, and moreover, the specification provides procedures for generating such

sequences. For example, as described in the specification at page 36, hybridization techniques are used to obtain synMuv DNA sequences, which are analyzed for the percent identity to a *lin-37* nucleotide sequence or a LIN-37 polypeptide, as described in the specification at pages 10-11.

In addition, the specification also clearly describes a number of distinguishing identifying characteristics of the nucleic acids of the claims, as amended herein, including the nucleotide and amino acid sequences of *lin-37*, functional characteristics of an identified nucleic acid, and methods of obtaining the desired nucleic acid sequences. Based on these factors, in combination with the level of skill and the knowledge in the art, one skilled in the art would conclude that Applicants were in possession of the invention as recited in claims 1, 7, 10, 16, 18, and 25, and claims 4-6, 11-15, and 17, which depend from and are therefore subject to the same limitations of claims 1, 7, 10, 16, 18, and 25. Thus, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 4-6, 10-18, and 25 stand rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite. The various aspects of this rejection are addressed below.

Claim 16 stands rejected for the recitation of "A cell which contains a substantially pure nucleic acid encoding a LIN-37 polypeptide..." on the assertion by the Examiner that a nucleic acid cannot remain substantially pure after being introduced into a cellular milieu.

In response to this rejection, Applicants direct the Examiner's attention to the specification at page 12, lines 8-10 which defines "substantially pure DNA" to be DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the DNA

of the invention is derived, flank the gene. Based on this definition, Applicants respectfully disagree that a nucleic acid can not remain "substantially pure" after being introduced into a cellular milieu. In light of these comments, withdrawal of this aspect of the rejection is respectfully requested.

Claims 1, 16, 18, and 25 stand rejected based on the recitation of "LIN-37," which the Examiner asserts is a laboratory designation. Claims 1, 16, 18, and 25 have been amended herewith to replace "LIN-37" with "lineage-37 (LIN-37)" in claims 1, 16, and 18, and to replace "*lin-37*" with "*lineage-37* (*lin-37*)" in claim 25. Accordingly, withdrawal of this aspect of the rejection is requested.

CONCLUSION

Applicants assert that the claims are now be in condition for allowance. Enclosed is a petition to extend the period for replying for three months, to and including March 12, 2000. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 12, 2001

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Version with Markings to Show Changes Made

1. (Twice Amended) A substantially pure nucleic acid encoding a lineage-37 (LIN-37) polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, said polypeptide having about 50% or greater amino acid sequence identity to SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

7. (Twice Amended) A substantially pure DNA encoding the amino acid sequence of SEQ ID NO: 1 that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, wherein said DNA encodes a polypeptide having the ability to alter cell proliferation.

10. (Twice amended) A substantially pure synMuv nucleic acid comprising nucleic acid having about 50% or greater nucleotide sequence identity to the DNA sequence of SEQ ID NO:2, wherein said nucleic acid encodes a polypeptide having the ability to alter cell proliferation.

16. (Twice Amended) A cell which contains a substantially pure nucleic acid encoding a lineage-37 (LIN-37) polypeptide that is free of the genes which, in the naturally-occurring genome of the organism, flank the gene, said polypeptide having about 50% or greater amino acid sequence identity to SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

18. (Twice Amended) A transgenic cell which contains a substantially pure nucleic acid encoding a lineage-37 (LIN-37) polypeptide having about 50% or greater amino acid sequence identity to SEQ ID NO: 1, wherein said polypeptide has the ability to alter cell proliferation.

25. (Twice Amended) A substantially pure *lineage-37* (*lin-37*) nucleic acid having about 50% or greater nucleotide sequence identity to SEQ ID NO: 2 isolated according to the method comprising:

(a) providing a cell sample;

(b) introducing by transformation into said cell sample a candidate *lin-37* nucleic acid;

(c) expressing said candidate *lin-37* nucleic acid within said cell sample; and

(d) determining whether said cell sample exhibits an altered cell proliferation response, whereby an altered level of cell proliferation identifies a *lin-37* nucleic acid.